VESTIBULAR MODULATION OF THE ABDUCTOR HALLUCIS AND THE ABDUCTOR DIGITI MINIMI MUSCLES IN RESPONSE TO CHANGES IN HEAD POSITION, VISUAL CUES, AND COGNITIVE DEMAND

by

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Maintaining standing balance involves processing of vestibular, visual, and somatosensory information to produce dynamic motor responses. Bilateral electrical vestibular stimulation (EVS) delivered through the mastoid processes can be used to explore the vestibular system. The purpose of this experiment was to determine if intrinsic foot muscles are modulated by vestibular activity and to elucidate any changes in the association between the vestibular stimulation and electromyography (EMG) responses in response to changes in head position, visual cues, and cognitive demand. Indwelling EMG of the abductor hallucis (AH) and abductor digiti minimi (ADM) were sampled while EVS was administered to quietly standing participants. The relationships between the EVS input and the muscle activity (output) were characterized in both the time and the frequency domains. When the head orientation was changed from left to right, the biphasic vestibular response in the time domain was inverted. In conditions including visual cues and increased cognitive demand, the vestibular responses demonstrated reduced and increased amplitudes of the coherence function, respectively. These findings indicate that the vestibular system modulates activity in the ADM and AH during quiet standing balance tasks.

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List of Acronyms

ADM: abductor digiti minimi
AH: abductor hallucis
cm: centimeter
EVS: electrical vestibular stimulation
MG: medial gastrocnemius
mA: milliamps
ms: milliseconds
mV: millivolts
s: seconds

Introduction

Importance of Investigating the Vestibular System

Healthy function of the vestibular system is an essential component of maintaining balance control. The ability to remain upright is an essential aspect of healthy function in humans. Falling is a major risk of injury, particularly in older adults with perhaps as many as one third of people older than 65 falling every year (Hausdorff et al. 2001). In 2013 alone, there were 2.5 million emergency room visits from falls, with direct medical expenses from falls exceeding $34 billion (CDC, 2015). There are several risk factors in older adults which increase their risk of falling, including muscle weakness, gait irregularities and balance impairments (Bradley 2011). Consequently, understanding balance control is of immense importance so that well-informed preventative training and rehabilitation strategies can be designed.

In healthy adults, maintaining standing balance involves processing and integration of vestibular, visual, and somatosensory information, with the contributions from each sensory system being weighted depending on both the environmental context and movement task (Horak 2006; Nashner & Berthoz 1978). Disorders in any of these three sources of sensory feedback may cause balance disorders, though the source of the damage dictates in which environmental contexts patients may be most vulnerable. When the vestibular system is dysfunctional, the ability to compensate when walking in dark conditions or upon unstable surfaces is decreased, making these contexts especially difficult to maintaining balance control. Severe loss of vestibular function can be

debilitating, and patients with lesions in the vestibular organs suffer from vertigo, destabilization of gaze, and decreased balance control (Strupp et al. 2006). Vestibular impairment has been reported to be an important contributing factor in up to 80% of patients who had experienced unexplained falls (Pothula et al. 2004).

Anatomy and Physiology of the Vestibular Apparatus

The vestibular apparatus is located in the inner ear, specifically in the otic capsule in the petrous portion of the temporal bone (Khan & Chang 2013). The vestibular apparatus contains five end organs: the superior, posterior, and horizontal semicircular canals which sense angular acceleration as well as two otolith organs, the utricle and the saccule, which sense linear acceleration of the head in the horizontal and vertical planes, respectively. The three semicircular canals are oriented orthogonally to each other so that angular acceleration in any direction may be detected (Fitzpatrick & Day 2004). The semicircular canals encode head motion through the mechanical disruption of small hair cells which are bent by endolymph fluid in the canals lagging head movement. The bending of these hair cells causes altered firing rates of primary sensory afferent neurons in the vestibulocochlear nerve (CN VIII). The otolith organs also work through bending small hair cells, though they accomplish the mechanical displacement via the movement of calcium carbonate crystals, which lag linear head accelerations relative to the hair cells (Hall & Guyton 2000). Once the mechanical stimuli in the vestibular apparatus has been transduced into an electrical signal, it is transmitted to the vestibular nuclei in the brainstem as well as to the fastigial nuclei and the most posterior lobe of the cerebellar vermis cerebellum. These nuclei are the first

synapse of the primary sensory afferent neurons in the vestibular nerve and they are the initial location at which the vestibular signal begins to be integrated with other inputs in order to generate an optimized corrective balance response (Angelaki & Cullen 2008). The early timing of the integration indicates that there is a high degree of convergence in the vestibular signal (Angelaki & Cullen 2008), meaning that information from the semicircular canals is integrated with the information from the otoliths as well as feedback from the visual and somatosensory systems (Rubin et al. 1975) and input from higher order brain structures (Horslen et al. 2014) at very early stages of transmission. Depending on the context of the integration of the vestibular signal in the vestibular nuclei, the signal may be sent to higher order brain structures, (*e.g.* the vestibular cortex), contribute to the stabilization of gaze via the vestibuloocular pathway (Sadeghi et al. 2011), or it may be transmitted down the vestibulospinal, corticospinal, and/or reticulospinal pathways to create a corrective balance response (Fitzpatrick & Day 2004; Britton et al. 1993).

Electrical Vestibular Stimulation (EVS) Responses

The first discovery of the potential for electrical stimulation to cause a balance disturbance most likely occurred in 1790 when Alessandro Volta passed a constant, direct current though his own head and toppled over as a result (Fitzpatrick & Day 2004). However, the vestibular mechanism of this response was not established until the work of Josef Breuer who delivered constant current stimulation to animals whose vestibular organs had been removed (Breuer 1875). The type of electrical stimulation used in these early experiments was developed over the years into a finely tuned technique known as galvanic vestibular stimulation, in which a direct current, low

voltage, square wave pulse is administered over the mastoid processes in order to generate a postural response. However, other variants of electrical vestibular stimulation, including sinusoidal waveforms and white noise stochastic signals are also used in exploring vestibular control of balance.

Stochastic electrical stimulation has been shown to generate postural reflexes (Pavlik et al. 1999), and similar responses can be obtained in leg muscles as when using galvanic vestibular stimulation (Dakin et al. 2007). However, there are several important advantages which make stochastic stimulation an attractive alternative to galvanic stimulation including shorter data collection periods, notably the ability to allow analysis of the vestibular-evoked balance response across a broad frequency domain through the calculation of coherence estimates, and decreased discomfort for participants (Dakin et al. 2007).

Electrical vestibular stimulation delivered over the mastoid processes bypasses the vestibular organs, stimulating the vestibular afferents at a retrolabrinthine location (Coats & Stoltz 1969; Watanabe et al. 1989). Bipolar, binaural electrical vestibular stimulation is performed by placing a cathode (negative electrode) and an anode (positive electrode) on the mastoid processes, causing the vestibular afferents on the cathodal side to increase their firing rate and the vestibular afferents on the anodal side to decrease their firing rate (Goldberg et al. 1984; Goldberg 2000). Electrical vestibular stimuli are interpreted as a true head acceleration where the perception of falling towards the cathode causes body sway in the direction of the anodal ear during a corrective balance response (Day et al. 1997; Coats & Stoltz 1969; Nashner & Wolfson 1974). The vestibular-evoked balance response is considered reflexive and involuntary

because expectation of EVS does not affect the postural response (Wardman et al. 2003). This was demonstrated when equivalent responses to EVS were produced regardless if the experimenter or the person receiving stimulation controlled the delivery of the EVS (Guerraz & Day 2005).

Vestibular-evoked balance reflexes can be characterized in both the time and frequency domains. In the time domain, the response occurs in two biphasic peaks within the muscles contributing to upright posture. The first peak, termed the short-latency peak, occurs ~50-70 ms in the leg (Fitzpatrick et al. 1994; Watson & Colebatch 1997; Dalton et al. 2014). The short-latency response is not considered part of the corrective balance response because it only produces transient sway which has no effect on trunk movement (Britton et al. 1993; Fitzpatrick et al. 1994). Rather, it is possible that the short-latency response represents the direct, unintegrated stimulation of the vestibulospinal pathway by the EVS, similar to how the short-latency component of the muscle stretch reflex represents a direct neural activation which is not modulated by voluntary intention of muscular activation (Reynolds 2010). The origin of the short-latency response remains a topic of active debate in the scientific community with much focus on merits of an otolith origin of the response (Cathers et al. 2005; Mian et al. 2010), and it has even been suggested that EVS delivered over the mastoid processes may be causing this portion of the postural response through non-vestibular pathways (Reynolds & Osler 2012).

The second phase of the vestibular myogenic response occurs at ~100-120 ms in the leg muscles and is known as the medium-latency response (Fitzpatrick et al. 1994; Watson & Colebatch 1997; Dalton et al. 2014). The medium-latency response is

opposite in polarity to the short-latency response. The medium-latency response is the corrective balance response which is necessary to keep the body upright after a head perturbation (Nashner & Wolfson 1974; Lund & Broberg 1983).

The difference in timing between the short- and medium-latency responses may be caused by the responses being transmitted down different spinal pathways. It has been proposed that the short-latency signal propagates down the vestibulospinal tract and the medium-latency propagates down the reticulospinal or corticospinal pathways (Britton et al. 1993), though the exact mechanism of propagation is not known. There is also some evidence that the vestibular-evoked balance response has two independent components from the otoliths and the semicircular canals which correspond to the short and medium-latency responses, respectively (Cathers et al. 2005). However, while the hypothesis that the semicircular canal input is responsible for the medium-latency response has been supported in other investigations, it is unlikely that otoliths are actually responsible for the short-latency response because there was no change in the direction of the vestibular-evoked response when comparing binaural vs. monaural stimulation which would have changed the acceleration signal from the otoliths (Mian et al. 2010).

The relationship between stochastic vestibular signals and EMG activity can also be observed in the frequency domain. Although the vestibular system is capable of modulating neck muscles at an operational frequency bandwidth of 0-70 Hz (Forbes et al. 2013; Forbes et al. 2015), the vestibular-evoked balance response in the leg occurs over a smaller frequency bandwidth of 0-20 Hz in healthy young adults with the reflexes containing characteristics resembling signals which have undergone low-pass

filtering (Dakin et al. 2007; Forbes et al. 2013). Since the physiological operational bandwidth of output frequencies of the vestibular apparatus is 0-20 Hz (Forbes et al. 2015), reflexes in the lower limbs account for the entire range of vestibular output under normal conditions.

Coherence is a linear measure of the relationship between EVS and the EMG responses in the frequency domain (Dakin et al. 2007); thus increased amplitudes of the coherence function may indicate an increased reliance on vestibular control. In situations where impairments to the balance system create a need to increase the relative importance of vestibular control of balance, such as when there are decrements in the function of other senses important for balance (Horak 2006), it may be reasonable to expect that increased coherence amplitudes would be observed.

The vestibular-evoked balance response is dependent on the need to maintain upright posture. Vestibular-evoked responses are not present in the lower limb muscles when a person is seated or when they are performing an equivalent balancing task to standing in which the head was held fixed and there was no the risk of falling (Fitzpatrick et al. 1994). Muscles which are tonically active, but not involved in maintaining balance do not exhibit a vestibular myogenic response (Britton et al. 1993; Forbes et al. 2015). Therefore, it appears that vestibular-evoked muscle responses only occur in those muscles important to maintaining the upright postural task.

The Intrinsic Foot Muscles

The intrinsic muscles of the foot, defined as those muscles which contain both their origin and insertion below the ankle joint (Moore et al. 2014), are important in movement and stability of the longitudinal arch, yet they have not been as extensively

investigated as other muscles of the leg. A dearth of information as to the importance and function of these muscles has contributed to the intrinsic foot muscles being overlooked in various clinical rehabilitation strategies, with external supports of the foot sometimes being used in place of training these muscles (McKeon et al. 2014).

The abductor hallucis (AH) is an intrinsic foot muscle on the medial aspect of the foot which originates on the medial process of the calcaneus, the flexor retinaculum, and the plantar aponeurosis and attaches on the medial side of the base of the proximal phalanx of the 1st digit (Moore et al. 2014). The AH accomplishes both flexion and abduction of the first metatarsophalangeal joint, and is responsible for acting in combination with other intrinsic foot muscles to control deformation of the longitudinal arch of the human foot (Kelly et al. 2014). Since increasing postural demand results in increased activation of the AH during a standing balance task (Kelly et al. 2012), it is plausible that vestibular input may be modulating the activity of this muscle.

It has been demonstrated that the AH is unique compared with other limb muscles in that it has relatively few motor units, 43 on average, compared with its cross sectional area (2.7cm^2) (Johns & Fuglevand 2011). Because of its low ratio of motor units to cross sectional area, the AH may have reduced precision in controlling gradation of force production (Enoka 1995), meaning that there may be limited ability to fine-tune precise movements with the AH. Also, the AH exhibits low mean peak motor unit discharge rates (14.0 ± 0.25 Hz) and is relatively resistant to fatigue (Kelly et al. 2013). While the fiber type composition of the AH has not been characterized in healthy adult humans, in healthy children 6-14, ~70% of muscle fibers in the AH were type 1 fibers (Sirca et al. 1990). Since these properties of the muscle are consistent with the necessity

of sustaining long-term stabilization of the longitudinal arch, they support the role of the AH as a postural muscle involved in maintaining quiet standing balance and foot stability.

Another intrinsic foot muscle, the abductor digiti minimi (ADM) originates on the medial and lateral processes of the calcaneus, the plantar aponeurosis, and the intramuscular septa and it attaches at the lateral side of the base of the proximal phalanx of the 5th digit (Moore et al. 2014). The abductor digiti minimi may play an important role during gait (Mann & Hagy 1979), but little is known about its role during upright postural control. Fiber type composition of the ADM has not been characterized. The ADM does exhibit higher peak motor unit discharge rates (range: 8-32 Hz) than the AH (range: 10-21 Hz) (Tanji & Kato 1973; Kelly et al. 2013), and other postural muscles such as the soleus (range: 5-20 Hz) (Dalton et al. 2009), which might indicate a slightly different functionality of the ADM compared to the AH.

It is unknown whether the activity of the intrinsic foot muscles is modulated by the vestibular system to maintain balance. In this study, the AH and ADM were chosen as representatives of the intrinsic foot muscles because of their surface proximity, and their respective medial and lateral respective anatomical locations which readily lend themselves to recording indwelling EMG. While it is unknown whether vestibular myogenic responses from the AH and ADM may be generalizable to other intrinsic foot muscles as a whole, the AH is involved in coordination with the quadratus plantae and the flexor digitorum brevis to stabilize the foot and contribute to balance control, and the AH demonstrates similar patterns of upregulated activation to the quadratus plantae and the flexor digitorum brevis with increasing postural demand during a balance task

(Kelly et al. 2012). Because of its low motor unit to surface area ratio, the AH may be an ideal model for studying the response of single motor units to vestibular stimulation. Indeed, it has been suggested that it may be possible to differentiate between the activities of single motor units up to very high contractile intensities and possibly even during maximum output of the AH (Johns & Fuglevand 2013).

Indwelling and Surface Electromyography

Electromyography (EMG) is a recording of the electrical activity of muscle tissue using surface electrodes placed on clean, dry skin (surface EMG) or fine wire electrodes inserted into the muscle belly itself (indwelling EMG). Electromyography is used both in research related to the fields of neuromuscular physiology and biomechanics as well as in clinical settings for the diagnosis of neuromuscular diseases. Surface electromyography is a non-invasive procedure in which the potentials of many motor units are recorded simultaneously. However, one of the limitations of surface EMG recordings is that recordings from small muscles may be influenced by cross-talk from nearby muscles. Multiunit fine wire electrodes reduce cross-talk and allow for cleaner recordings from muscles such as the AH and ADM.

Head position and balance control

The anatomical location of the vestibular apparatus in the inner ears causes the vestibular-evoked balance responses to be dependent on head position. When the head is oriented in the forward direction, postural responses primarily occur in the mediolateral direction (Pavlik et al. 1999), but when the head is oriented to the left or right, responses are directed in the anterior-posterior direction (Lund & Broberg 1983;

Cathers et al. 2005). In a seminal study (Nashner and Wolfson, 1974), it was found that when the anode faced posteriorly, the plantar flexors had increased excitation, whereas when the anode faced anteriorly, the plantar flexors had decreased excitation. Hence, the direction of the vestibular-evoked response in the plantar flexors inverts by changing position of the head from turned over the left shoulder to turn over the right. (Nashner & Wolfson 1974; Lund & Broberg 1983). Changes in head position may also impact the amplitude of the vestibular myogenic responses because they may align or misalign to the direction of the response with the action of a particular muscle (Day & Fitzpatrick 2005; Iles & Pisini 1992).

In this experiment, the effect of changing head position from facing left to right was examined in order to observe whether this would cause the vestibular-evoked balance reflex to be inverted in the ADM and AH, thereby supporting or rejecting vestibular origin of the muscular response.

Visual feedback and balance control

It has been known for many years that the removal of visual feedback increases postural sway (Edwards 1946). Removing visual cues has also been shown to increase the background EMG level and the size of the vestibular-evoked balance response (Fitzpatrick et al. 1994). The medium-latency amplitude is increased when visual input is removed (Britton et al. 1993; Fitzpatrick & Day 2004). Short-latency responses have been shown to have no change with visual input in one investigation (Britton et al. 1993), but in others there has been an increase in short-latency peak amplitude when the eyes are closed (Welgampola & Colebatch 2001; Fitzpatrick et al. 1994).

In this study, the effects of visual cues were tested in order to examine whether the vestibular myogenic responses in the AH and ADM were modulated by inputs from other sensory systems.

Cognitive tasks and balance control

Changing cognitive demand may play an important role in balance related activities (Teasdale et al. 1993; McIlroy et al. 1999; Brown et al. 1999). Investigating balance during simultaneous administration of a secondary cognitive task may provide a realistic approximation of challenges associating with maintaining balance control during activities of daily life. A secondary cognitive task is a task which increases cognitive demand while a primary task (*i.e.* maintaining standing balance) is being performed. This attentional split forces cognitive resources to be divided, leading to decreased performance on one or both tasks (Bourke 1996; Pashler 1994). In other words, adding a secondary cognitive task in a balance paradigm can cause increased instability in some circumstances or declining performance on a cognitive task assessment in others (Schaefer et al. 2009). However, while increasing cognitive demand has been linked to increased postural sway in young adults (Pellecchia 2003), this association disappears when center of pressure and center of mass measurements are normalized to anxiety and arousal levels (Kerr et al. 1985; Maki & McIlroy 1996).

Despite its minimal effects on whole-body postural outcome measures in young adults, increasing cognitive demand has been linked to neuromuscular impairments which could impact balance control. For instance, there was increased duration of the latency period before activation of reactive EMG responses to balance perturbations

during periods of increased cognitive demand (McIlroy et al. 1999). Additionally, increased cognitive demand has been associated with greater intra-cortical inhibition (Holste et al. 2015). Consequently, it seems probable that during cognitive demand, there may be other compensatory mechanisms occurring (such as upregulating the vestibular response to balance perturbations) which may help preserve balance function despite these impairments. An upregulation of the vestibular response could be reflected in greater vestibular myogenic response amplitudes in both the frequency and time domains with increased cognitive demand.

In this experiment, changes in the vestibular evoked balance responses in the AH and ADM were examined in order to determine if the vestibular myogenic response could be modulated by changes in cortical activity.

Purpose and Hypotheses

The purpose of this experiment was to determine if intrinsic foot muscles, specifically the AH and ADM, are modulated by vestibular activity and to examine if there are changes in the vestibular myogenic response in both the frequency and time domains in response to changes in head position, visual cues, and by performing a cognitive task. There were four primary hypotheses for this experiment: 1) a significant coherence trace as well as the biphasic short- and medium-latency responses would be present in the foot muscles when EVS was delivered to a blindfolded participant with head turned to the left; 2) when the head was turned to the right instead of the left, the direction of the short- and medium-latency responses would invert and the amplitudes of the short-latency response, medium-latency response, and the coherence function would decrease; 3) the addition of visual input would not change the short-latency

response, but the amplitude of the medium-latency response and coherence function would be decreased; 4) when a secondary cognitive task was performed, the amplitude of the short-latency response amplitude would not change while the medium-latency response and the coherence function would be greater than in the single-task condition.

Methods

Participants

Three men (height: 180.1 ± 9.5 cm, weight: 72.2 ± 8.2 kg, and age 28 ± 6.7 years old) and four women (height: 173.4 ± 2.4 cm, weight: 66.3 ± 5.0 kg, and age 23 ± 3.1 years old) volunteered for this experiment. All participants were healthy with no known history of cardiovascular disease, neurological diseases, musculoskeletal impairments, or balance disorders. After verbal and written explanation of the experimental procedures, each participant granted oral and written informed consent. All procedures conformed to the *Declaration of Helsinki* and were approved by the University of Oregon's institutional review board for human research.

Vestibular stimuli

Two carbon rubber electrodes (~12 cm^2) were used to administer the electrical vestibular stimulation after being coated with Spectra 360 electrode gel (Parker Laboratories, Fairfield, NJ). The electrodes were positioned in a binaural, bipolar fashion over the mastoid processes (anode left/cathode right) and secured with Durapore tape (3M innovations, St. Paul, MN) and an elastic headband. The EVS signals were generated offline using LabVIEW (National Instruments, Austin, TX) and were delivered as analogue signals through a data acquisition board (*p*XIe-1082, National Instruments, Austin, TX) to a constant current biphasic constant current stimulator (DS5, Digitimer, Welwyn Garden City, UK). The stimuli consisted of white noise stochastic signals delivered in 120-s trials with randomized peak-to-peak

amplitudes of up to 3 mA and a root-mean-square amplitude of 1.37 mA. The frequency of the EVS also varied randomly over a bandwidth of 0-20 Hz.

Data Collection

Surface EMG from the medial gastrocnemius (MG) was collected with self-adhesive electrodes (Blue Sensor M-00-S/50, Ambu, Ballerup, Denmark) placed with a ~1 cm edge to edge inter-electrode distance on muscle belly. A ground electrode for the surface EMG was placed over the medial condyle of the tibia. Multiunit intramuscular EMG from the ADM and AH was collected in the right foot using indwelling EMG electrodes. These electrodes were custom-made by the investigator using insulated fine wire (Stablohm 800 A, California Fine Wire Company, Grover Beach, CA). The tips of each recording area was stripped in order to expose ~2 mm of recording area. Two indwelling EMG electrodes were inserted in a bi-polar arrangement into the muscle bellies of the AH (directly inferior to the medial malleolus) and the ADM (distal to the tuberosity of the 5^{th} metatarsal) with an inter-electrode distance of ~2 cm. Hypodermic needles (Exel International Medical Products 27 G 1.5") were used to insert the fine wire electrodes while the participant was seated. Before insertion, all fine wire electrodes and hypodermic needles were sterilized using a table-top, low temperature, ethylene oxide sterilization system (Anprolene AN74i, Andersen Products, Haw River, NC) and the insertion site was thoroughly cleaned with rubbing alcohol. Once a fine wire electrode had been inserted into the target muscle, the hypodermic needle was removed carefully so that the recording area of the fine wire electrodes would remain in the muscle tissue. A ground electrode for the indwelling EMG was placed over the lateral malleolus. After the setup of the surface and indwelling EMG, each participant

underwent at least one 30-s EVS familiarization trial during which it was confirmed that clean EMG recordings were being obtained from the indwelling electrodes in the ADM and AH.

Cognitive Task

The cognitive task used in this study was time-limited arithmetic, in which participants were allowed a maximum of ten seconds to add or subtract randomly generated two digit integers. Twelve questions were presented orally by the investigator per 120-s trial. The number of errors as well as the amount of time delay before answering were recorded.

Testing Protocol

The experimental setup is displayed in Figure 1. Baseline cognitive task performance was assessed while the participant was relaxed and seated both before and after the standing balance protocol. The remainder of the protocol was performed with arms relaxed at sides, feet positioned with 4-6 cm separating the medial malleoli, and the head positioned 90º to either to the left or right. This head orientation maximized the effect of the vestibular stimulation in producing anterior posterior sway, thus aligning the response with the action of the ankle muscles (Cathers et al. 2005; Day & Fitzpatrick 2005; Mian & Day 2009). Foot position was marked with chalk so that it would remain constant throughout the experiment. The head was tilted so that Reid's plane was oriented ~19º above horizontal in order to align the direction of the net vestibular response was aligned around a roll axis in the horizontal plane (Day & Fitzpatrick 2005). A laser pointer secured above the right ear was used mark head

position on a target so that it could be maintained during the course of the experiment. During trials without visual cues, participants were instructed to maintain head position with verbal feedback from an investigator. In order for a vestibular-evoked response to appear in a muscle, it must be actively engaged in maintaining standing balance; thus participants were instructed to lean slightly forward in order to ensure that the AH and ADM would remain engaged throughout the protocol.

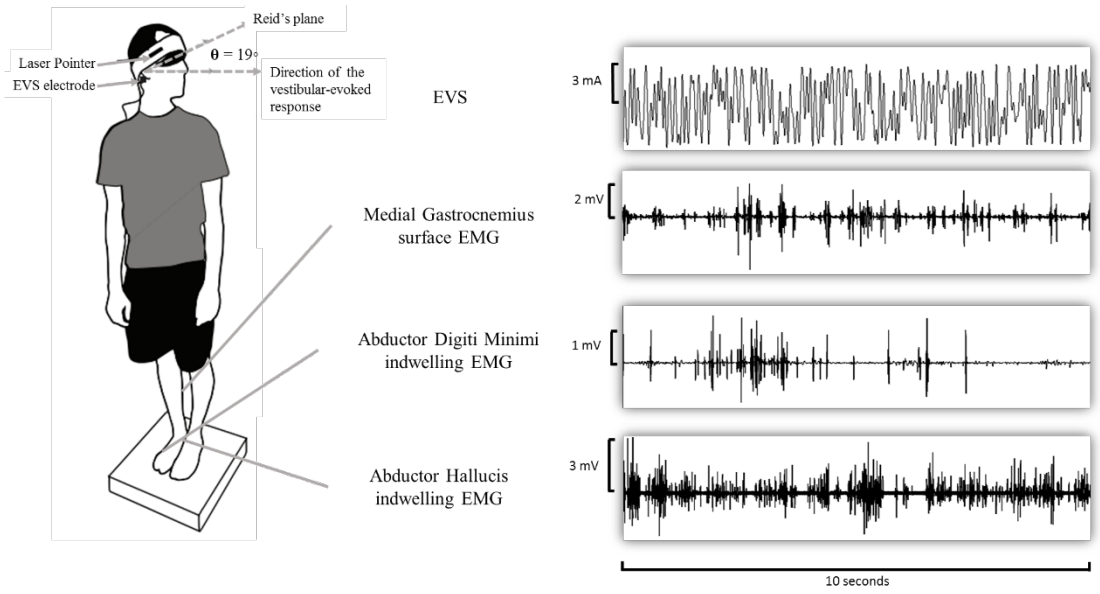

Figure 1: Experimental setup during the blindfolded head left condition.

A laser was secured to a headband and oriented to Reid's plane on the right side of the head. The head was tilted so that Reid's plane was oriented 19º above horizontal in order to align the direction of the vestibular-evoked response with the horizontal plane (Day & Fitzpatrick 2005). Ten second traces of the unprocessed electrical vestibular stimulation (EVS), surface electromyography (EMG) from the medial gastrocnemius, indwelling EMG from the abductor digiti minimi, and indwelling EMG from the abductor hallucis are displayed to the right.

After blindfolded subjects performed a 120-s single-task control trial without EVS, four conditions were performed in which EVS was delivered: 1) standing

blindfolded with head left, 2) standing with head right and vision removed, 3) standing with the head left with visual feedback, 4) standing and performing a secondary cognitive task with head left and eyes closed. The order of these four conditions was randomized. In order to reduce discomfort for participants, each condition consisted of two 120-s trials for a total of 240-s per condition. Between trials, participants were allowed rest at any time upon request.

Data Analysis

The EMG signals were pre-amplified (x1000; NeuroLog Digitimer NL844 Pre-Amplifier, Welwyn Garden City, UK), amplified (x2 NeuroLog Digitimer NL900D, Welwyn Garden City, UK), band pass filtered (30-1000 Hz), and sampled at 2048 Hz. Surface and indwelling EMG signals were zero-phase digitally high pass filtered at 30 Hz in MATLAB (MathWorks, Natick, MA). All EMG and EVS signals were digitized with an analog-to-digital converter (National Instruments, BNC – 2090A) and stored on a PXI until transferred to an external hard drive.

The EMG recorded during each trial was full-wave rectified and time-locked to the onset of the EVS. The two 119-s data records for each condition were then concatenated for each participant to produce a single 238-s data record for each of the four conditions per individual. Cumulant density and coherence functions, calculated in MATLAB, were derived from a multivariate Fourier analysis (1-s segment length and 1 Hz resolution; NeuroSpec 2.0: http://www.neurospec.org) as described in Rosenberg et al. 1989 and Halliday et al. 1995.

Coherence is the linear relationship between the EMG and EVS signals in the frequency domain, defined on a scale from 0 to 1 (Rosenberg et al. 1989; Halliday

1995; Dakin et al. 2007). Analyzing coherence allows for comparison of the operational bandwidths of the vestibular myogenic response across different muscles or task conditions. After being calculated for each participant, the coherence estimates for all participants were concatenated for each condition.

Cumulant density function is similar to a cross-correlation like histogram which represents the relationship between the EMG and EVS signals in the time domain (Dakin et al. 2007). The correlative nature of the cumulant density function indicates that the relationship it characterizes is associative and not necessarily causative (Dakin et al. 2010). Cumulant density amplitudes were expressed as correlation coefficients bounded by -1 and 1 because they had been normalized by the product of the vector norms of the EVS and EMG signals (Rosenberg et al. 1989; Halliday 1995; Dakin et al. 2010).

Statistical Analysis

The coherence and cumulant density functions were determined to be significantly different than zero if they exceeded the 95% confidence limits based on the number of disjoint segments in the estimation (Rosenberg et al. 1989; Halliday 1995). The effect of head position, visual cues, and stance was compared using the difference of coherence test (NeuroSpec 2.0) in MATLAB to determine the bandwidths in which the coherence of one experiment was significantly different than another, with significance defined as those values exceeding a 95% confidence interval (Rosenberg et al. 1989; Amjad et al. 1997).

The peak amplitudes of the short- and medium-latency responses for each participant were analyzed and the mean values were compared between conditions,

respectively using paired, two-tailed t-tests and Cohen's d as a measure of effect size. The change in performance on the cognitive task was also analyzed with paired, two tailed t-tests and Cohen's d. Data were reported as means ± standard deviations and significance was set at $p < 0.05$.

Results

The Frequency Domain

The EVS to EMG coherence function for the MG, ADM, and AH gained statistical significance in all subjects for all four experimental conditions (see Figure 2 for an example of single subject data). The bandwidth of coherent frequencies in the MG, ADM, and AH maintained a similar range (0-20 Hz) across all four conditions (Figure 3-5). The difference in coherence function between head left and head right condition demonstrated that the head left orientation produced significantly greater coherence over a bandwidth of 2-20 Hz in the MG (Figure 3A), over 0-12 Hz in the ADM (Figure 4A), and over 7-9 and at 17 Hz in the AH (Figure 5A). The difference in coherence function between the eyes open and eyes closed conditions showed that no vision caused significantly greater coherence at low frequencies in the MG (0-2 Hz; Figure 3B), the ADM (0-2 Hz; Figure 4B), and the AH (0-5 Hz; Figure 5B). The difference in coherence, when the elevated cognitive demand condition was compared with the single-task condition, demonstrated that the increased cognitive demand condition had significantly greater coherence in the MG (2, 4 and 7-8 Hz; Figure 3C), the ADM (2-5 and 7-11 Hz; Figure 4C), and the AH (3, 11, and 14 Hz; Figure 5C).

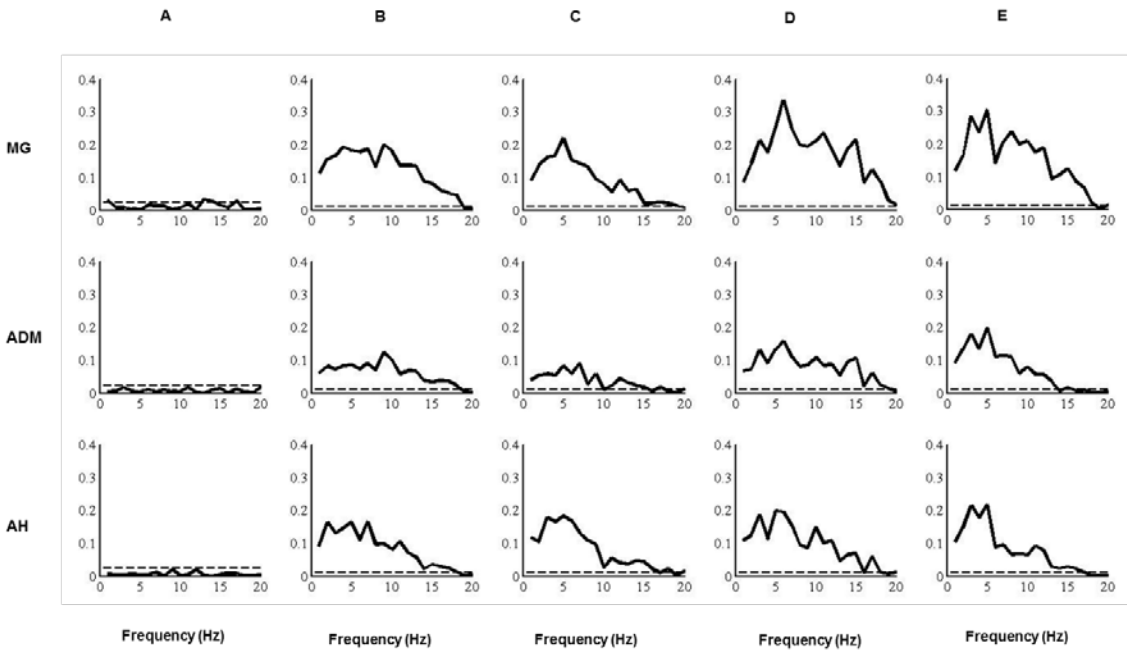

Figure 2: Vestibular-evoked responses in the frequency domain (coherence) in the medial gastrocnemius (MG), abductor digiti minimi (ADM), and abductor hallucis (AH) for a representative individual subject.

A, Blindfolded and head turned to the left with no vestibular stimulation. *B*, Blindfolded and head left. *C*, Blindfolded and head right. *D*, Head left with vision. *E*, Blindfolded and head left with a secondary cognitive task. The coherence function reached significance in all conditions beyond a 95% confidence interval (horizontal dashed line).

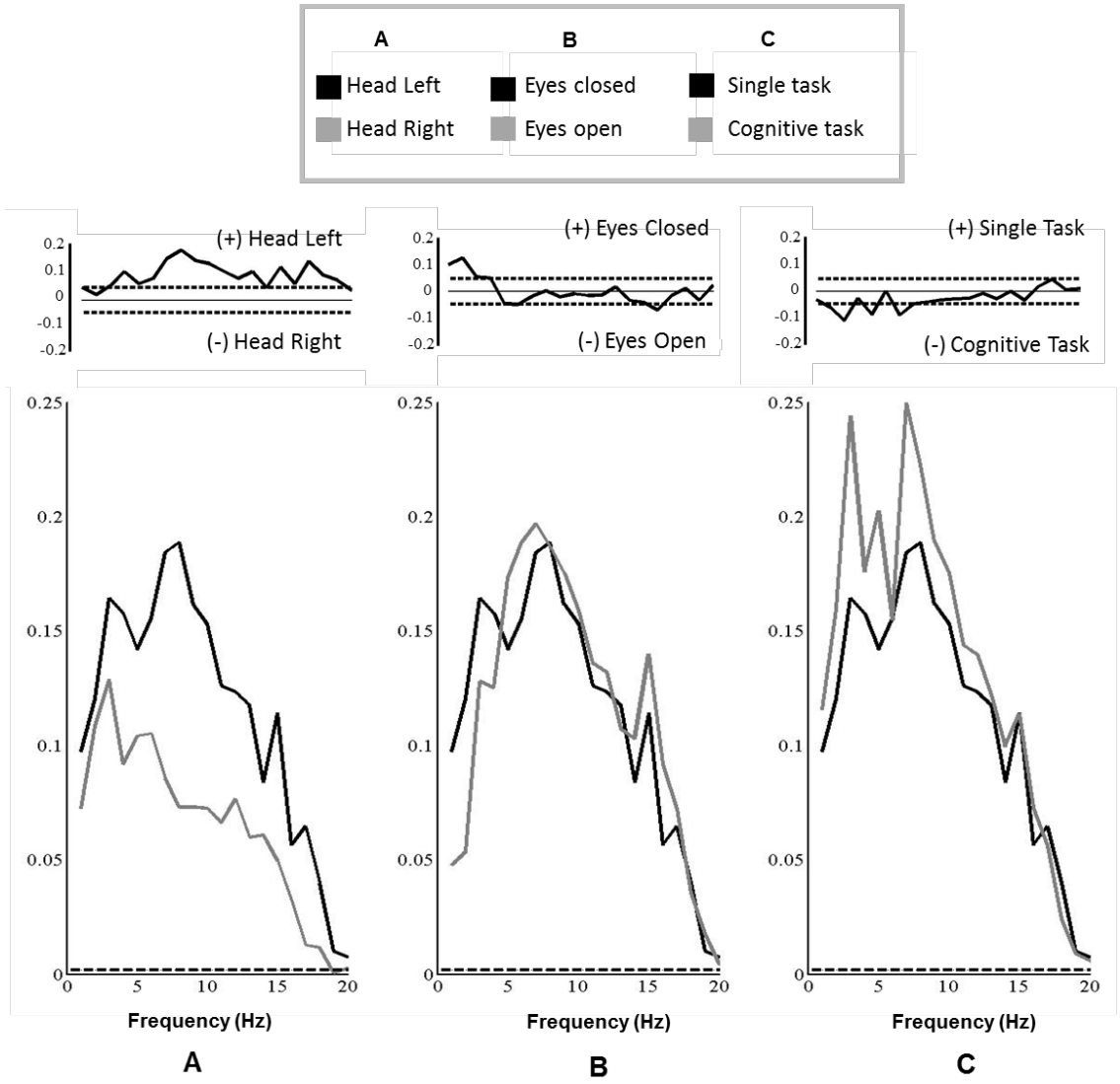

Figure 3: Concatenated coherence (bottom) and difference of coherence (top) estimates in the medial gastrocnemius.

A, Responses in the blindfolded, head left condition (black) and in the blindfolded, head right condition (gray). *B*, Responses in the blindfolded, head left condition (black) and in the head left and vision condition (gray). *C*, Responses in the blindfolded, head left condition (black) and in the blindfolded, head left and cognitive task condition (gray). The dashed horizontal lines indicate 95% confidence limits.

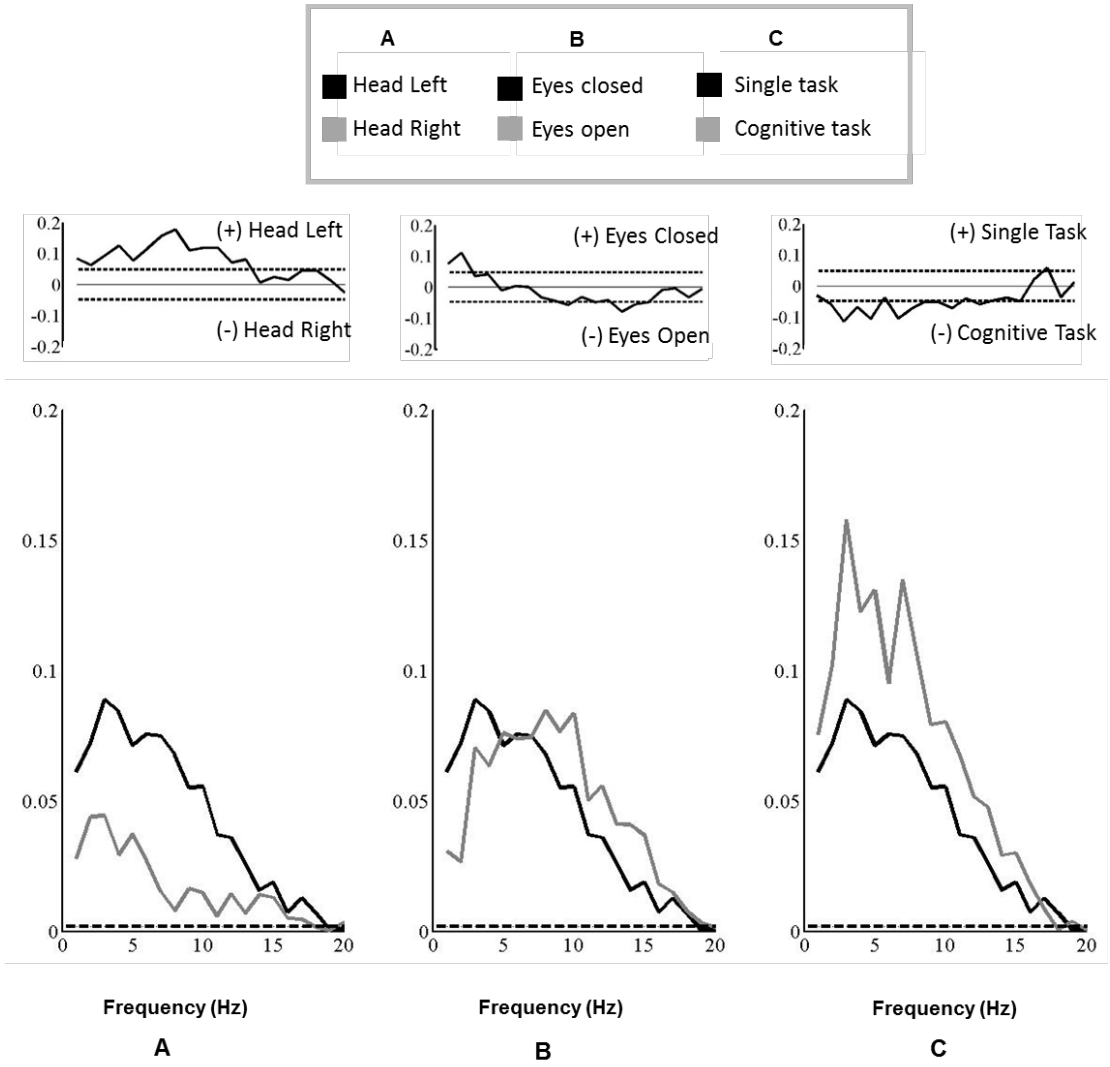

Figure 4: Concatenated coherence (bottom) and difference of coherence (top) estimates in the abductor digiti minimi.

A, Responses in the blindfolded, head left condition (black) and in the blindfolded, head right condition (gray). *B*, Responses in the blindfolded, head left condition (black) and in the head left and vision condition (gray). *C*, Responses in the blindfolded, head left condition (black) and in the blindfolded, head left and cognitive task condition (gray). The dashed horizontal lines indicate 95% confidence limits.

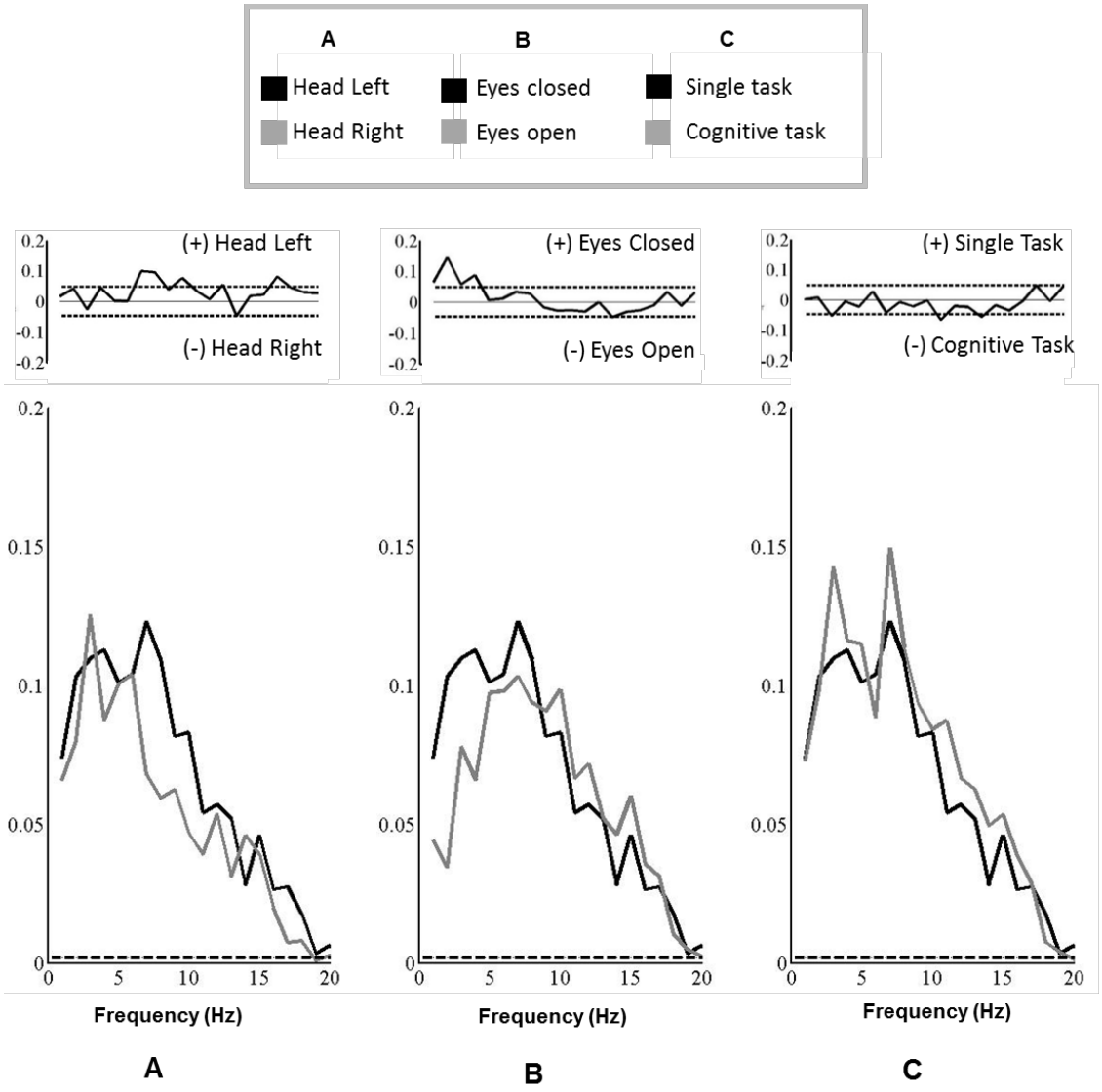

Figure 5: Concatenated coherence (bottom) and difference of coherence (top) estimates in the abductor hallucis.

A, Responses in the blindfolded, head left condition (black) and in the blindfolded, head right condition (gray). *B*, Responses in the blindfolded, head left condition (black) and in the head left and vision condition (gray). *C*, Responses in the blindfolded, head left condition (black) and in the blindfolded, head left and cognitive task condition (gray). The dashed horizontal lines indicate 95% confidence limits.

The Time Domain

The EVS to EMG cumulant density function for the MG, ADM, and AH gained significance for all subjects during all four experimental conditions (see Figure 6 for an example of single subject data). The short-latency peak amplitude when the head was turned to the left was opposite in polarity and was 46, 60, and 39% larger than the short-latency peak when the head was turned to the right in the MG ($p < 0.05$, d = 21.58; Figure 7A), the ADM ($p < 0.05$, d =6.80; Figure 8A), and the AH ($p < 0.05$, d =14.26; Figure 9A), respectively. However, there were no significant changes in the short-latency peak amplitude when comparing eyes open and closed in the MG, ADM or AH ($p = 0.07$, 0.70, and 0.34, respectively; Figure 7-9 B). Likewise, altering cognitive demand conditions did not change short-latency peak amplitudes in any muscle of interest ($p = 0.43$-0.70; Figure 7-9 C). The medium-latency peak amplitude for the head left condition was opposite in polarity and was 31, 50, and 17% larger than head right for the MG ($p < 0.05$, d = 9.58; Figure 7A), ADM ($p < 0.05$, d = 6.53; Figure 8A), and AH ($p < 0.05$, d = 9.68; Figure 9A), respectively. The medium-latency peak amplitude in the blindfolded condition was 17, 24, and 13% larger than the medium-latency peak amplitude when visual feedback was available in the MG ($p < 0.05$, d = 4.07), ADM ($p < 0.05$, d = 4.11), and AH ($p < 0.05$, d = 2.72), respectively. The medium-latency peak during single-task conditions was 14 and 12% smaller than the medium-latency peak when cognitive demand was increased in the MG ($p < 0.05$, d = 4.36) and ADM ($p < 0.05$, d = 4.64), with a 15% decrease possibly trending in the AH ($p = 0.10$).

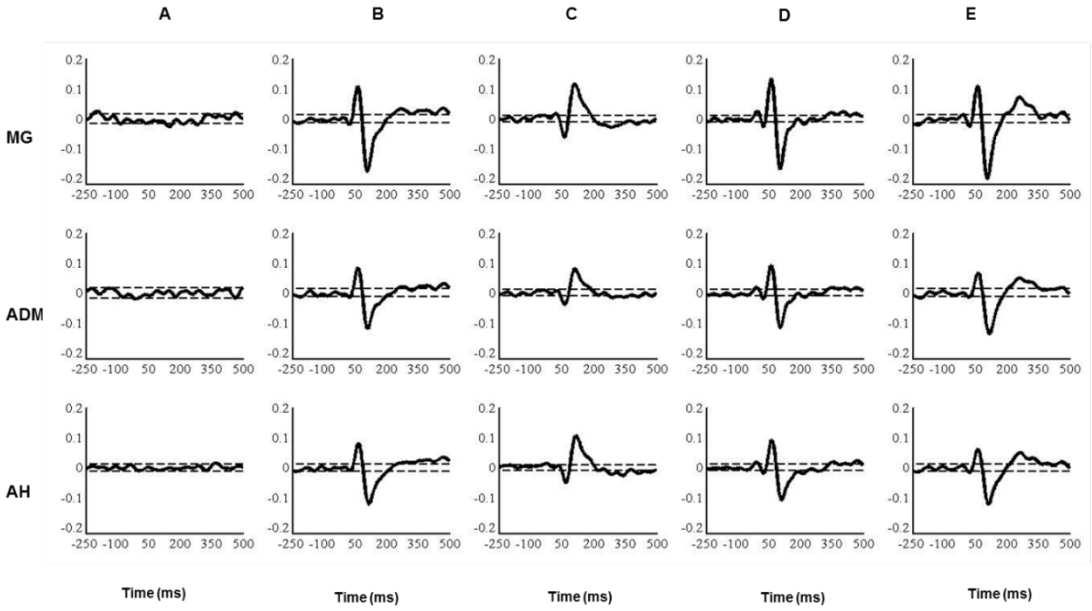

Figure 6: Vestibular-evoked responses in the time domain (cumulant density) in the medial gastrocnemius (MG), abductor digiti minimi (ADM), and abductor hallucis (AH) for a representative individual subject.

A, Blindfolded and head turned to the left with no vestibular stimulation. *B*, Blindfolded and head left. *C*, Blindfolded and head right. *D*, Head left with vision. *E*, Blindfolded and head left with a secondary cognitive task. Both peaks of the biphasic response reached significance in all conditions beyond a 95% confidence interval (horizontal dashed lines).

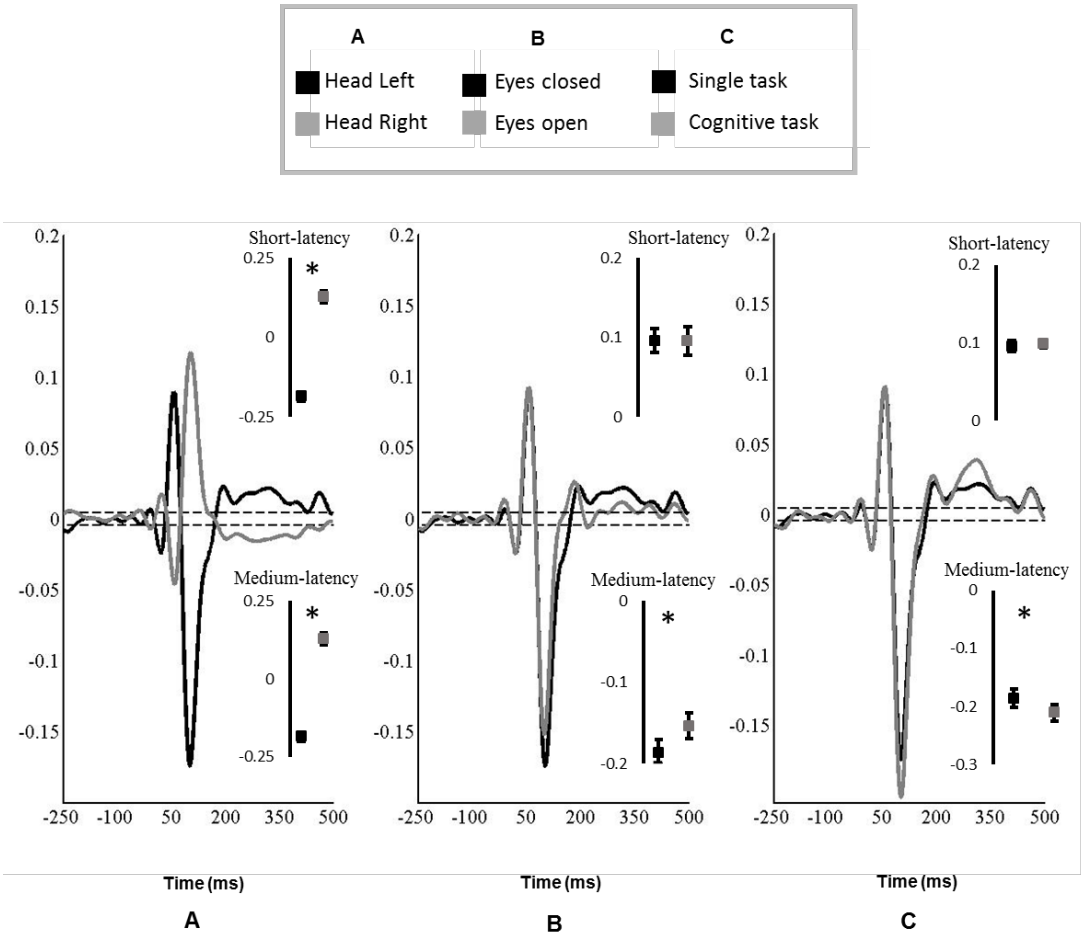

Figure 7: Concatenated cumulant density estimates in the medial gastrocnemius.

Peak amplitude of the short latency (top) and medium-latency (bottom) peaks are displayed on the left side of each tracing with standard error bars included. Significant changes in peak amplitude between conditions ($p < 0.05$) were denoted with asterisks (*). *A*, Responses in the blindfolded, head left condition (black) and in the blindfolded, head right condition (gray). The biphasic vestibular-evoked response reversed polarity when head position was flipped ($p < 0.05$). *B*, Responses in the blindfolded, head left condition (black) and in the head left and vision condition (gray). The medium-latency response was significantly larger in the blindfolded condition ($p < 0.05$). *C*, Responses in the blindfolded, head left condition (black) and in the blindfolded, head left and cognitive task condition (gray). The medium-latency response was significantly larger in the cognitive task condition ($p < 0.05$). Dashed horizontal lines indicate 95% confidence intervals.

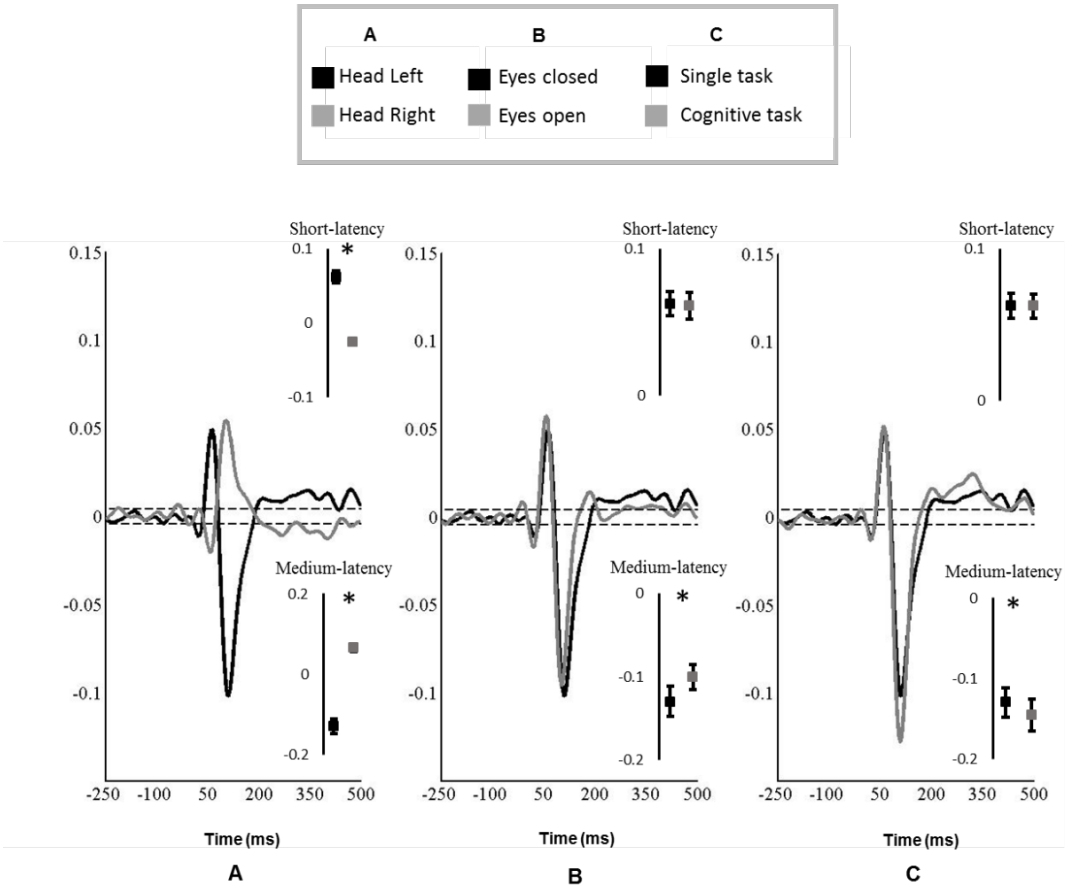

Figure 8: Concatenated cumulant density estimates in the abductor digiti minimi.

Peak amplitude of the short latency (top) and medium-latency (bottom) peaks are displayed on the left side of each tracing with standard error bars included. Significant changes in peak amplitude between conditions ($p < 0.05$) were denoted with asterisks (*). *A*, Responses in the blindfolded, head left condition (black) and in the blindfolded, head right condition (gray). The biphasic vestibular-evoked response reversed polarity when head position was flipped ($p < 0.05$). *B*, Responses in the blindfolded, head left condition (black) and in the head left and vision condition (gray). The medium-latency response was significantly larger in the blindfolded condition ($p < 0.05$). *C*, Responses in the blindfolded, head left condition (black) and in the blindfolded, head left and cognitive task condition (gray). The medium-latency response was significantly larger in the cognitive task condition ($p < 0.05$). Dashed horizontal lines indicate 95% confidence intervals.

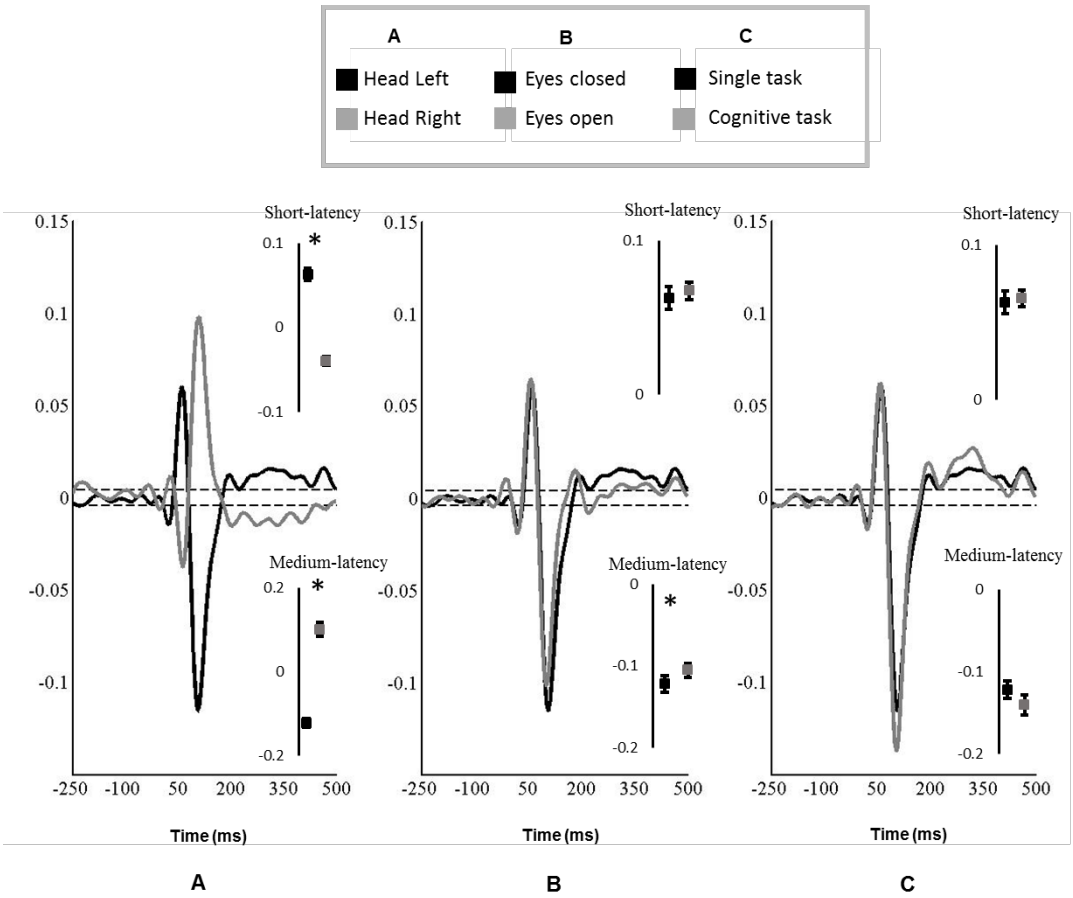

Figure 9: Concatenated cumulant density estimates in the abductor hallucis.

Peak amplitude of the short latency (top) and medium-latency (bottom) peaks are displayed on the left side of each tracing with standard error bars included. Significant changes in peak amplitude between conditions ($p < 0.05$) were denoted with asterisks (*). *A*, Responses in the blindfolded, head left condition (black) and in the blindfolded, head right condition (gray). The biphasic vestibular-evoked response reversed polarity when head position was flipped ($p < 0.05$). *B*, Responses in the blindfolded, head left condition (black) and in the head left and vision condition (gray). The medium-latency response was significantly larger in the blindfolded condition ($p < 0.05$). *C*, Responses in the blindfolded, head left condition (black) and in the blindfolded, head left and cognitive task condition (gray). The medium-latency response was significantly larger in the cognitive task condition ($p < 0.05$). Dashed horizontal lines indicate 95% confidence intervals.

Cognitive Task Results

There was no difference in the time needed to answer the arithmetic questions between the baseline cognitive task (6.76 ± 3.09-s) and the cognitive task during EVS (6.33 ± 3.12-s; $p = 0.18$). There were also no changes in the cognitive task accuracy ($p = 0.90$) when comparing the baseline (7.5 ± 2.9 correct out of 12) and EVS (7.6 ± 2.9 correct out of 12) conditions.

Discussion

The goal of this experiment was to determine whether intrinsic foot muscles are modulated by vestibular activity during standing balance and to examine if there are changes in vestibular-evoked balance response in both the frequency and time domains in response to changes in head position, visual cues, and cognitive demand. We found that vestibular-evoked balance responses could be obtained in both the AH and ADM using stochastic electrical vestibular stimulation at a maximum peak to peak amplitude of ±3 mA. Significant coherence (0-20 Hz) was demonstrated for all muscles in each condition (Figures 3-5), corroborating previous reports of a 0-20 Hz bandwidth EVS-EMG coherence in the MG in young people (Dakin et al. 2007; Dalton et al. 2014). . The vestibular origin of the muscular responses was supported by the inversion of the biphasic time-domain responses following a shift in head position from left to right (Figure 7-9A). Additionally, it appears that changes to the vestibular-evoked response in the AH and ADM occur in a similar pattern to the MG when engaged during a balance task.

The amplitude of the coherence function as well as both peaks of cumulant density function were decreased in head right compared with head left (Figures 7-9A). This occurred because when the head was turned to the right, the direction of the corrective balance response was in the anterior direction compared with being in the posterior direction when the head was turned to the left. Therefore, since increasing activation of the gastrocnemius produces movement to the posterior direction during a standing balance reflex (Iles & Pisini 1992), activation of MG is lower in the head right condition. Because the reflexes in the AH and ADM were in the same direction as the

MG (Figures 7-9), it is probable that activation of these muscles increased during the vestibular-evoked response to produce sway in the posterior direction when the head was turned to the left and the anodal electrode stimulated the left vestibular nerve.

The addition of visual input did not change the amplitude of the short-latency response in comparison to the blindfolded condition, corroborating a previous report which indicated no change in the short-latency response (Britton et al. 1993) while standing, in contrast to others which report a decrease in the short-latency response with visual cues (Welgampola & Colebatch 2001; Fitzpatrick et al. 1994). The magnitude of the medium-latency response was reduced, consistent with previous findings in Soleus EMG (Fitzpatrick et al. 1994; Britton et al. 1993) and center of pressure responses (Bent et al. 2002). Removal of visual information caused significantly higher coherent amplitudes and was associated with lower coherence at low frequency bandwidths in the MG (0-2 Hz), the ADM (0-2 Hz), and the AH (0-5 Hz). Because of mechanical low pass filtering, postural sway is limited to < 2 Hz (Dakin et al. 2010; Fitzpatrick et al. 1996). Consequently, changes in the frequency domain caused by visual cues at these low bandwidths may indicate a mechanism for the increases in postural sway observed in other reports (Fitzpatrick & Day 2004) when the eyes are closed. Although it has been reported that all stimulus frequencies in the bandwidth 0-20 Hz contribute to both the short- and medium-latency peaks (Dakin et al. 2011), the short-latency response operates predominantly at characteristically high frequencies (>10 Hz) while the medium-latency response tends to operate at frequencies less than 10 Hz (Dakin et al. 2007; Dakin et al. 2010). Thus, the change at low frequencies but not at high frequencies in the difference of coherence function (Figures 3-5 B) supports the change

in the medium-latency response as well as the lack of change in the short-latency response (Figures 7-9 B).

When the secondary cognitive task was performed, the amplitude of the medium-latency response increased by 17, 24, and 13% in the MG, ADM, and AH, respectively, while the amplitude of the short-latency peak amplitude was unaltered for any muscle (Figures 7-9 C). The coherent frequencies between the EVS and the EMG tended to be larger with increased cognitive demand, with significant changes being manifested in multiple interspersed peaks predominantly occurring below 11 Hz (Figures 4-6 C). Given the lack of change in the short-latency amplitude and the elevated medium-latency amplitude during increased cognitive demand, the change in the coherence function at low frequencies corroborates our findings with the manipulation of visual cues in supporting the hypothesis that the medium-latency response is composed primarily of lower frequencies while the short-latency response is composed primarily of higher frequencies. Moreover, the finding that elevated cortical demand and lack of visual input increase the corrective response to a vestibular error signal at predominantly lower frequencies suggests that there are likely different origins of the short- and medium-latency responses.

The increase in the low frequency coherence amplitudes and increased medium-latency amplitudes with no visual feedback and increased cognitive demand may be caused by an increased reliance on the vestibular system (Day et al. 2002). This increased sensitivity to vestibular signals may be due to increased excitability at the vestibular nuclei (Horslen et al. 2014; Naranjo et al. 2016).

A limitation of this experiment included the non-continuous nature of the cognitive task. Due to ranging skill base and comfort level and with math-based questions, there may have been differences in the amount of cognitive resources needed by each participant to complete the cognitive task. There was a wide range in the amount of time needed to answer the math questions (3.7-8.5-s average time before answering in baseline cognitive task). Since the questions were delivered every 10-s, this allowed some participants several seconds between their responses to the questions whereas other participants had far less time. However, despite this limitation, we were still able to demonstrate changes in the vestibular myogenic response occurring with increased cognitive demand.

The effect of performing cognitive tasks appears to vary with age. Difficult cognitive tasks augment regularity in gait patterns in young adults (20-30 years old), but leads to greater irregularity in adults 70-80 years old (Verrel et al. 2009). While introducing a cognitive task may not cause decreased balance control in young adults, it might affect older adults differently because they may have decreased dynamic sensory compensatory mechanisms than those available to young adults (Li et al. 2001; Peters 2016). Since performance on tasks involving both cognitive and balance demands is significantly lower in older adults with a history of falls (Makizako et al. 2013), studying age-related differences in cognitive demand may be a very important topic of future investigation. Due to the low ratio of motor units to cross sectional area in the AH, it may be an optimal model in which to study the cellular responses of single motor units (Johns & Fuglevand 2011). Now that the vestibular myogenic reflex has been demonstrated in the AH, a next step could be examining mechanisms underlying age-

related changes in the reflex with increasing cognitive demand at the level of single cell responses using the AH as a model.

It has been demonstrated that the MG provides an excellent model for measuring vestibular-evoked balance responses as the reflexes are easily recordable (Dakin et al. 2007; Nashner & Wolfson 1974). By investigating the vestibular myogenic responses in the MG, AH, and ADM, it was possible to observe patterns in how each muscle was modulated under various task conditions. In all three muscles, the vestibular response displayed very similar patterns of change when head position, visual input and cognitive demand were varied. For instance, the medium-latency peak amplitude was significantly altered when each independent variable was modified while the short-latency peak amplitude was unchanged in the vision and cognitive demand comparisons in all three muscles (Figures 7-9). Moreover, similar patterns emerged in coherence tracings for each muscle. Orienting the head to the right and adding visual cues caused a decrease in coherence amplitudes while increasing cognitive demand tended to increase coherence with pockets of significance (Figures 3-6). Therefore, although there are important differences in the precise function and physical properties of the MG and intrinsic foot muscles, the similarities in the muscular responses across different task conditions reported here may indicate that previous research in the MG (Fitzpatrick & Day 2004; Dakin et al. 2007; Forbes et al. 2015; Dalton et al. 2014; Nashner & Wolfson 1974; Mian et al. 2010; etc.) might have a high degree of relevance in informing our knowledge of vestibular control of the AH and ADM.

Conclusion

The findings of this study demonstrate that the vestibular system is able to modulate activity in the abductor hallucis and abductor digiti minimi during standing. This experiment extends the previously reported operational bandwidth of coherent frequencies in the MG (0-20 Hz) (Dakin et al. 2007; Dalton et al. 2014) to intrinsic foot muscles. Elevated cortical demand and lack of visual input increase the corrective response to a vestibular error signal at predominantly lower frequencies, indicating that there are likely different origins of the short- and medium-latency responses. The abductor hallucis and the abductor digiti minimi are likely important contributors to upright standing balance control and they are capable of dynamic vestibular responses which can be modulated by other sensory feedback as well as by cortical activity.

Glossary

Abductor digiti minimi: a muscle located on the lateral side (i.e. outside) of the foot.

Abductor hallucis: a muscle located on the medial side (i.e. inside) of the foot.

Afferent: a sensory nerve which carries information towards the central nervous system.

Brainstem: the central trunk of the mammalian brain.

Center of pressure: the point where the total sum of pressure acts on the body.

Coherence: a linear measure of the relationship between EVS and the EMG responses in the frequency domain.

Concatenate: to link or pool together.

Cumulant density: a function is similar to a cross-correlation like histogram which represents the relationship between the EMG and EVS signals in the time domain

Electrical vestibular stimulation: an electrical stimulus which causes the vestibular nerve to send signals as if there were an involuntary head movement.

Electromyography: a recording of the electrical activity of a muscle.

Gastrocnemius: one of three calf muscles, located in the leg.

Medium-latency response: the second motor response to electrical vestibular stimulation occurring at ~ 110 ms.

Motor Unit: a motor neuron and all skeletal muscle fibers which are innervated by said motor neuron.

Reid's plane: a line extending from the inferior margin of the orbit to the auricular point and then to the center of the occipital bone.

Short-latency response: the first motor response to electrical vestibular stimulation occurring at ~ 60 ms.

Stochastic: randomly determined.

Vestibular-evoked balance response: the postural response elicited from electrical vestibular stimulation.

Vestibular myogenic response: the postural response in muscle elicited from electrical vestibular stimulation.

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